IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	: Annapragada, et al.	Examiner	: Perreira, Melissa Jean
Application No.	: 10/830,190	Group Art	: 1618
Filing Date	: 21 April 2004	Docket No.	: 27428-4
Confirmation No.	: 7714		
Title	: Compositions and Methods for Enhancing Contrast in Imaging		

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REPLY BRIEF

Sir/Madam:

Pursuant to 37 C.F.R. § 41.41, Appellant submits this Reply Brief in connection with the above-referenced application. The appeal is from the decision of the Examiner mailed November 21, 2007, rejecting claims 1-4, 6-11, and 25-33. This Reply Brief, filed within two months of the Examiner's Answer, along with a Certificate of Electronic Filing, is timely filed. The fees required under 37 C.F.R. § 41.20 have been paid.

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I. STATUS OF CLAIMS

Claims 1-4, 6-11, 25, 26,[1] and 27-33 stand rejected under 35 U.S.C. 103(a) as being obvious over Torchilin et al. (Biochim. Biophys. Acta 1996, 1279, 75-83) (Appeal Brief, Section IX, Evidence Appendix, Tab C) ("Torchilin") in view of Payne et al. (U.S. Patent No. 4,744,989) (Appeal Brief, Section IX, Evidence Appendix, Tab D) ("Payne") and further in view of Sachse et al. (Invest. Radiol. 1997, 32, 44-50) (Appeal Brief, Section IX, Evidence Appendix, Tab E) ("Sachse") or Leike et al. (Invest. Radiol. 2001, 36, 303-308) (Appeal Brief, Section IX, Evidence Appendix, Tab F) ("Leike").

[1] In its Appeal Brief, Appellant noted that no basis for rejection was given for claim 26. (Appeal Brief, at p. 4). In the Examiner's Answer, the Examiner explained that the omission was a "typographical error," and that claim 26 was, in fact, rejected on the same bases as claims 1-4, 6-11, 25, and 27-33. (Examiner's Answer, at p. 10).

II. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Whether claims 1-4, 6-11, and 25-33 are unpatentable under 35 U.S.C. 103(a) as being obvious over Torchilin in view of Payne and further in view of Sachse or Leike.

III. ARGUMENT

The science here is demanding. But the legal bases under which claims may be rejected are certain. The Office does not show that the appealed claims are rendered obvious by the various references of record; and it is clear that the Office has not afforded proper weight to Appellant's rebuttal evidence.

For the following reasons set forth below supplementing those in the Appeal Brief, Appellant respectfully requests that the subject claims now be passed to allowance. First, the Examiner has improperly failed to consider the totality of the art. Second, the cited art fails to disclose or render obvious a method for making the claimed liposomes, which precludes a conclusion of obviousness of the claimed liposomes. Third, the Examiner's "obvious to try" rationale is improper because the Examiner cannot demonstrate any reasonable expectation of success. Finally, the Examiner's reliance on Torchilin is improper because Torchilin is not analogous art.

A. The Examiner Has Improperly Failed To Consider The Totality Of The Art.

The Examiner has taken an improper pick-and-choose approach to the cited references and the art in general, ignoring, among other things, the teachings that counsel strongly away from the claims of the subject application.

"A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention." (W.L. Gore & Assoc., Inc. v. Garlock, Inc., 721 F.2d 1540, cert. denied, 469 U.S. 851 (1984); M.P.E.P. § 2141.02(VI)). "A prior art reference that 'teaches away' from the claimed invention is a significant factor to be considered in determining obviousness . . . ." (M.P.E.P. § 2145(X)(D)(1)). "It is improper to combine references where the references teach away from their combination." (M.P.E.P. § 2145(X)(D)(2); In re Grasselli, 713 F.2d 731, 743 (Fed. Cir. 1983)). Indeed, "[t]he totality of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is evidence of nonobviousness." (In re Hedges, 783 F.2d 1038 (Fed. Cir. 1986); M.P.E.P. § 2145(X)(D)(3)).

"Known disadvantages in old devices which would naturally discourage search for new inventions may be taken into account in determining obviousness." (U.S. v. Adams, 383 U.S. 39 (1966)).

There can be no question that at the time the present application was filed, the "accepted wisdom in the art" was that the invention claimed in the subject application was unachievable, undesirable, or both. The Examiner does not appear to have given any weight to this "accepted wisdom."

Generally speaking, the claims of the subject application recite liposomes having a very, very small size (less than 150 nm), which encapsulate: (1) a nonradioactive contrast enhancing agent; (2) a sterically bulky excipient such as cholesterol; (3) at least one lipid or phospholipid; and (4) at least one lipid or phospholipid which is derivatized with a polymer chain (also known as a "stealth lipid").

One of the four references maintained by the Examiner, namely Sachse, specifically teaches that the inclusion of a stealth lipid into a liposome that encapsulates nonradioactive contrast enhancing agent leads to a "drastic increase in vesicle size" of the liposome:

> Subsequently, surface-modification [of Iopromide-carrying liposomes] was performed by simple mixing with the respective PEG-derivative overnight. In the case of DSPE-PEG this procedure was accompanied by a **drastic increase in vesicle size. Thus, the resulting mean diameter amounted to 204 nm compared to 132 for the unmodified** . . . .

(Sachse, at p. 3, para. 8) (emphasis added). Based on the teachings of Sachse, the achievement of the claimed liposome compositions—i.e., having both nonradioactive contrast enhancing agent and polymer-derivatized lipids or phospholipids, and having a mean diameter of less than 150 nm, is not obvious.[2]

[2] On this basis, Appellant takes particular exception to the Examiner's unsupported statement that "the encapsulation of the contrast agents of Payne et al. into the liposomes of Torchilin et al. will have predictable results . . . ." (Examiner's Answer, at p. 6). Indeed, at the relevant time period, a person having ordinary skill in the art would have predicted a "drastic increase in vesicle size" of the liposome—and not the very small liposomes of the subject application.

In addition, the Examiner completely ignores Appellant's arguments regarding U.S. Patent No. 6,217,849 issued to Tournier et al. ("Tournier"). Tournier teaches vesicles in the 200 nm to 1 μm range, with an average diameter of 400 nm. (Tournier, col. 4, l. 60-67). Tournier clearly teaches away from the use of the small liposomes of the subject application:

> The use of tiny liposome vesicles of the kind proposed in EP-A-0 442 962 for the delivery of drugs (in the order of 50 nm or less) are [sic] therefore **unpractical for blood-pool imaging**. Much **the same applies to** the proposals of Gabison et al. in Biochim. Et Biophys. Acta 1103 (1992) 94-100 and I.A.J.M. Bakker-Woudenberg et al. ibid 318-326 directed to **liposomes with an average size between 0.07 μm and 0.1 μm** and prolonged residence times in the blood.

(Tournier, at col. 3, l. 14-22) (emphasis added). Tournier also teaches away from the use of polymer-derivatized liposomes. (Id., at col. 3, l. 30-35):

> [T]he production of liposomes with the "stealth factors" is rather cumbersome. In addition, "**stealth factored" liposomes are known to have very low entrapment capacity** and while such liposomes may be suitable to carry specific drugs, and therefore useful in therapy, they **are almost useless in imaging**.

(Id., col. 3, lines 30-35) (emphasis added).[3]

The age of a reference is relevant where it provides evidence that "the art tried and failed to solve the problem." (In re Wright, 569 F.2d 1124, 1127). Tournier post-dates three of the four references cited by the Examiner, namely Torchilin, Sachse, and Payne (Payne was cited against Tournier). Thus, Tournier, a person having skill in the art, who had the benefit of the teachings of Torchilin, Sachse, and Payne, specifically taught that stealth factors (i.e., polymer-derivatized lipids and phospholipids) are "almost useless in imaging," and that small liposomes "have very low entrapment capacity" and are "unpractical for blood pool imaging."

The one reference cited by the Examiner that does not pre-date Tournier is Leike. But Leike, reflecting the "accepted wisdom in the art," expressly excluded polymer-derivatized liposomes and liposomes having a mean diameter of less than 200 nm. (Leike, at pp. 305, 306).

[3] It should be noted that liposomes containing polymer-derivatized lipids, such as those of the subject application, are often referred to in the art as "stealth factored" liposomes.

The totality of the art must be considered. The Examiner does not appear to have afforded the "accepted wisdom in the art" any weight, instead picking and choosing among the art that which the Examiner ostensibly believes supports the Examiner's position. This is in error.

For at least the foregoing reasons, claims 1-4, 6-11, and 25-33 are not obvious over Torchilin in view of Payne and further in view of Sachse or Leike, and the rejections under 35 U.S.C. § 103(a) should be reversed.

B. The Cited Art Fails To Disclose Or Render Obvious A Method For Making The Claimed Liposomes, Which Precludes A Conclusion Of Obviousness Of The Claimed Liposomes.

The Examiner has not cited a reference or combination of references that disclose or render obvious a method for making the claimed liposomes, i.e., liposomes having a very, very small size (less than 150 nm), which encapsulate: (1) a nonradioactive contrast enhancing agent; (2) a sterically bulky excipient such as cholesterol; (3) at least one lipid or phospholipid; and (4) at least one lipid or phospholipid which is derivatized with a polymer chain.

"A conclusion of obviousness requires that the reference(s) relied upon be enabling in that it put the public in possession of the claimed invention." (M.P.E.P. § 2145). The court in In re Hoeksma, 399 F.2d 269, 274 (CCPA 1968), stated:

> Thus, upon careful reconsideration it is our view that if the prior art of record fails to disclose or render obvious a method for making a claimed compound, at the time the invention was made, it may not be legally concluded that the compound itself is in the possession of the public. In this context, we say that the absence of a known or obvious process for making the claimed compounds overcomes a presumption that the compounds are obvious, based on close relationships between their structures and those of prior art compounds.

(See also Ashland Oil, Inc. v. Delta Resins & Refractories, Inc., 776 F.2d 281, 295, 297 (Fed. Cir. 1985); In re Grose, 592 F.2d 1161, 1168 (CCPA 1979) ("Failure of the prior art to disclose or render obvious a method for making any composition of matter, whether a compound or a

mixture of compounds like a zeolite, precludes a conclusion that the composition would have been obvious.")).

The references cited by the Examiner, either alone or combination, do not disclose or render obvious a method for making liposomes having a very, very small size (less than 150 nm), which encapsulate: (1) a nonradioactive contrast enhancing agent; (2) a sterically bulky excipient such as cholesterol; (3) at least one lipid or phospholipid; and (4) at least one lipid or phospholipid which is derivatized with a polymer chain. Indeed, Torchilin teaches the external transchelation of a radioactive tracer to DTPA, not the encapsulation of a nonradioactive contrast enhancing agent. While Sachse accomplishes at least partial encapsulation of the nonradioactive contrast enhancing agent, Sachse experienced a drastic increase in vesicle size upon the attempted encapsulation of the phospholipid which is derivatized with a polymer chain where the liposome also encapsulated a nonradioactive contrast enhancing agent. Leike, taking into account the "accepted wisdom in the art," did not even attempt to encapsulate the phospholipid which is derivatized with a polymer chain into a liposome that also encapsulated a nonradioactive contrast enhancing agent.

The Examiner attempts to bridge this gap with Payne. But Payne also does not teach or even suggest a liposome having lipids or phospholipids which are derivatized with a polymer. Moreover, the examples of Payne almost exclusively demonstrate liposome sizes of several microns. See, e.g., Examples 1 (5.3 μm) (Id., at col. 8, l. 56), 2 (2.5 μm) (Id., at col. 9, l. 15), 3 (5.3 μm) (Id., at col. 9, l. 40), 4 (2.5 μm) (Id., at col. 9, l. 67), and 7 (1.8 μm, 2.0 μm, 3.1 μm, and 4.25 μm) (Id., at col. 12, l. 33 and col. 13, l. 22, 60, 62). In Example 7, Payne refers to liposomes (composed of DMPC/DMPG/AmB) with "mean sizes of 100 to 150 nm" (Id., at col. 13, l. 24), but those liposomes indisputably: (1) are not polymer derivatized; (2) do not contain cholesterol; and (3) do not contain non-radioactive contrast enhancing agent. In short, the Examiner's implication that Payne teaches the ready manipulation of the size of relevant

liposomes is incorrect.[4] Rather, Payne represents another example of the Examiner picking and choosing so much of a reference as to support the Examiner's untenable obviousness position.

In sum, the cited art fails to disclose or render obvious a method for making the claimed liposomes, which precludes a conclusion of obviousness of the claimed liposomes. For at least the foregoing reasons, claims 1-4, 6-11, and 25-33 are not obvious over Torchilin in view of Payne and further in view of Sachse or Leike, and the rejections under 35 U.S.C. § 103(a) should be reversed.

C. The Examiner's "Obvious to Try" Rationale Is Improper Because The Examiner Cannot Demonstrate Any Reasonable Expectation Of Success.

The Examiner's "obvious to try" rationale is improper because the examiner does not and cannot establish any reasonable expectation of success.

"An 'obvious to try' rationale may support a conclusion that a claim would have been obvious where one skilled in the art is choosing from a finite number of identified, predictable solutions, **with a reasonable expectation of success.**" (M.P.E.P. § 2145(X)(B) (emphasis added); see also In re O'Farrell, 853 F.2d 894, 903 (Fed. Cir. 1988) (holding that the claimed method would have been obvious over the prior art relied on because one reference contained a detailed enabling methodology, a suggestion to modify the prior art to produce the claimed invention, and evidence suggesting the modification would be successful)).

As set forth above, the cited art does not contain an enabling methodology. For this reason alone, the Examiner's "obvious to try" rationale is improper.[5] In addition, the Examiner

[4] The Examiner states that "[t]he reference of Payne et al. was . . . used to teach liposomes of sizes 100 nm to 6 μm . . . may encapsulate a nonradioactive iodinated contrast agent." (Examiner's Answer, at p. 8). Payne does not teach this. That is why the Examiner cannot point to a single actual instance in Payne of a liposome encapsulating a nonradioactive iodinated contrast agent and having a size below 150 nm. Again, the Examiner has improperly picked and chosen those portions of the art that the Examiner believes support the Examiner's position.

[5] This is true notwithstanding the Examiner's boilerplate statement that "it is obvious to vary and/or optimize the amount of (compound) provided in the composition, according to the guidance provided by (reference), to provide a composition having the desired properties such as the desired (ratios, concentrations, percentages, etc.)." (Examiner's Answer, at p. 7).

cannot credibly assert the existence, at the time of the invention, of a "reasonable expectation of success." As set forth above, Tournier post-dates three of the four references cited by the Examiner, namely Torchilin, Sachse, and Payne. Tournier, a person having skill in the art, who had the benefit of the teachings of Torchilin, Sachse, and Payne, specifically taught that stealth factors (i.e., polymer-derivatized lipids and phospholipids) are "almost useless in imaging," and that small liposomes "have very low entrapment capacity" and are "unpractical for blood pool imaging." And Sachse experienced a "drastic increase in vesicle size" upon the attempted encapsulation of a phospholipid which is derivatized with a polymer chain, where the liposome also encapsulated a nonradioactive contrast enhancing agent. The one reference cited by the Examiner that does not pre-date Tournier is Leike. But Leike, reflecting the "accepted wisdom in the art," expressly excluded polymer-derivatized liposomes and liposomes having a mean diameter of less than 200 nm. Notwithstanding the Examiner's hind-sight-driven picking and choosing from the cited art, there is simply no basis to suggest that a person having ordinary skill in the art at the relevant time would have had a reasonable expectation of success in the combination of Torchilin, Payne, Sachse, and Leike.

For at least the foregoing reasons, claims 1-4, 6-11, and 25-33 are not obvious over Torchilin in view of Payne and further in view of Sachse or Leike, and the rejections under 35 U.S.C. § 103(a) should be reversed.

D. The Examiner's Reliance On Torchilin Is Improper Because Torchilin Is Not Analogous Art.

Torchilin is not analogous art and, thus, the Examiner's continued reliance on Torchilin is improper.

"Under the correct analysis, any need or problem known in the field of endeavor at the time of the invention and addressed by the patent [or the application at issue] can provide a reason for combining the elements in the manner claimed." (KSR Int'l Co. v. Teleflex Inc., 82 USPQ2d 1385, 1397 (2007); M.P.E.P. § 2141.01(a)(I)). In other words, for art to be analogous,

it must be in the field of the Appellant's endeavor or reasonably pertinent to the problem to be solved.

Appellant's field of endeavor is the preparation of liposomes having a nonradioactive contrast enhancing agent encapsulated therein, the liposomes being useful for enhancing contrast of one or more areas of a subject for X-ray imaging. The problem addressed by the subject application is to prepare the liposomes in a very, very small size (less than 150 nm), while still encapsulating: (1) a nonradioactive contrast enhancing agent at sufficiently high concentrations (e.g., at least 30 milligrams of iodine per milliliter of the suspension of liposomes) to allow for clinically useful image contrast enhancement; (2) a sterically bulky excipient such as cholesterol; (3) at least one lipid or phospholipid; and (4) at least one lipid or phospholipid which is derivatized with a polymer chain.

As explained in Appellant's Appeal Brief at pp. 9-10, Torchilin is not within Appellant's field of endeavor. Rather, Torchilin addresses biodistribution of liposomes in acutely damaged tissues with broken-down vascular and cell membrane barriers. The primary goal of Torchilin is to characterize immunoliposomes, specifically those that have antibodies to myosin on their exterior. (Torchilin, at Abstract, p. 76). To accomplish this goal, Torchilin seeks to determine antibody-liposome immunoreactivity by direct binding of radiolabeled antibody-liposome and antibody-liposome-polymer conjugates. (Id., at p. 77). Torchilin does not teach or suggest liposomes having a nonradioactive contrast enhancing agent encapsulated therein. Indeed, Torchilin does not teach a contrast enhancing agent at all. This is because Torchilin is not directed to enhancing contrast of one or more areas of a subject for X-ray imaging. Rather, Torchilin affirmatively teaches a radioactive tracer—In^{111}, externally trans-chelated to DTPA, thereby providing a remarkably different structure and function of the liposomes of Torchilin compared to the liposomes of the subject application. It cannot be overemphasized that the use of radioactive In^{111} allows for detection to occur at tracer concentrations that are orders of magnitude lower than that required for encapsulated, nonradioactive contrast enhancing agents. Structural and functional differences such as those which are extant between the Torchilin

liposomes and the liposomes of the subject application carry great weight in the determination of "non-analogy." (M.P.E.P. § 2141.01(a)(II); In re Ellis, 476 F.2d 1370, 1372 (CCPA 1973)).

For the same reasons, Torchilin does not address the problem to be solved—that is, Torchilin does not teach the preparation of liposomes in a very, very small size (less than 150 nm), that encapsulate: (1) a nonradioactive contrast enhancing agent in high concentrations; (2) a sterically bulky excipient such as cholesterol; (3) at least one lipid or phospholipid; and (4) at least one lipid or phospholipid which is derivatized with a polymer chain.

The Examiner does not dispute these facts. (Examiner's Answer, at p. 7-8). As such, the Examiner's reliance on Torchilin is improper.

For at least the foregoing reasons, claims 1-4, 6-11, and 25-33 are not obvious over Torchilin in view of Payne and further in view of Sachse or Leike, and the rejections under 35 U.S.C. § 103(a) should be reversed.

E. Conclusion.

Appellant respectfully asserts that the case is now in a condition for allowance for the reasons set forth in the Appeal Brief and on the grounds that: (1) the Examiner has improperly failed to consider the totality of the art; (2) the cited art fails to disclose or render obvious a method for making the claimed liposomes, which precludes a conclusion of obviousness of the claimed liposomes; (3) the Examiner's "obvious to try" rationale is improper because the Examiner cannot demonstrate any reasonable expectation of success; and (4) the Examiner's reliance on Torchilin is improper because Torchilin is not analogous art.

While no additional fees are believed due, the Commissioner is hereby authorized to charge any additional fees, or credit any overpayment, to Deposit Account No. 02-2051, referencing Attorney Docket No. 27428-4.

Respectfully submitted,

Dated: November 4, 2008

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